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Research With Cognitively Impaired Participants

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Abstract

Illnesses that cause cognitive impairment are a considerable health problem in the United States. These include Alzheimer's disease, Huntington's chorea, cerebrovascular disease, psychiatric disorders, chronic alcoholism, and AIDS dementia complex. Illness associated with cognitive impairment may cause great suffering to the affected patients and their families. Research involving individuals who may be at risk for or have cognitive impairment is necessary to improve our understanding of these illnesses. For example, this may occur during efforts to develop effective therapies to treat them. However, research with participants who have cognitive impairment presents additional ethical concerns because they may be vulnerable to coercion. Therefore, nurse researchers must not only understand the principles of informed consent (i.e., autonomy, beneficence, nonmaleficence, and justice), but also the additional safeguards provided in the common rule to protect cognitively impaired participants in research. These safeguards include advanced informed consent, legal representative, and assent. Gaps exist in federal regulations related to adhering to these safeguards such as how to assess for decision-making capacity and variations on who can be a legal representative. The nurse researchers have potential roles as educators and advocates in research involving participants with cognitive impairment.

Keywords

informed consent; vulnerable populations; cognitively impaired; code of federal regulations; safeguards; decision making capacity

Illnesses that cause cognitive impairment are a considerable health problem in the United States. These include Alzheimer's disease, Huntington's chorea, cerebrovascular disease, psychiatric disorders, chronic alcoholism, and AIDS dementia complex (National Institutes of Health, 2006). Illness associated with cognitive impairment may cause great suffering to the affected patients and their families (Alzheimer's Association, 2004). Research involving individuals who may be at risk for or have cognitive impairment is necessary to improve our understanding of these illnesses. For example, this may occur during efforts to develop effective therapies to treat them (Alzheimer's Association, 2004; Dukoff & Sunderland, 1997). The federal government provides funding for such research studies; however additional ethical issues arise for participants with cognitive impairment because cognitive impairment limits the individual's ability to provide their personal consent to participate in research. The purpose of this paper is to examine the unique ethical concerns raised in research involving cognitively impaired persons. Further, what does a budding nurse researcher or practitioner need to know to provide safeguards to protect the rights of those with cognitive impairment? To better understand this issue, a definition of cognitive impairment is needed.

Cognitive impairment is defined as:

having either a psychiatric disorder (e.g. psychosis, neurosis, personality or behavior disorders) an organic impairment (e.g. dementia) or a development disorder (e.g. mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependant on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests (National Institutes of Health, 2006).

Based on this definition, there is concern, for example, that a mildly cognitively impaired individual could be vulnerable to coercion. Secondly, individuals with severe cognitive impairment may lack the capacity to provide consent (Institutional Review Board, Arizona, 2005). Capacity is defined as the “ability of an individual to understand the choices presented, to appreciate the implications of choosing one alternative or another, and to make and communicate a decision” (UCLA, Policy 24: Special Subjects Populations: Cognitively Impaired, 2007, p. 2). This definition is enhanced by a closer look at informed consent in general, the core elements and principles underlying the concept of informed consent, and how these are related to research participants who may be cognitively impaired. Additionally, this paper includes a review of federal mechanisms that have been put in place to ensure appropriate conduct of research and protection of these individuals. These mechanisms or safeguards include advanced informed consent, durable power of attorney (or substituted decision-making) or a legal representative, and assent. An overview of current gaps in regulations related to research with cognitively impaired persons is provided.

Informed Consent: Elements and Guiding Principles

Luce (2003) provided this definition of informed consent, “an autonomous authorization of individuals of a medical intervention or involvement in research” (p. S153). He added that there are five elements of the informed consent. First, individuals giving consent must be able to make medical decisions (i.e., are competent). Secondly, information about the study must be disclosed to them in a manner relevant to them and their situation. Third, individuals giving consent must be able to receive and comprehend the information. Fourth, their consent must be voluntary, or free from undue influence or coercion. Last but not least, the individuals must be able to provide formal authorization to be treated or included in clinical investigation. For example, Alzheimer disease affects cognitive abilities, including memory, judgment, comprehension, and reasoning, all of which are necessary to understand the informed consent process (Dukoff & Sunderland, 1997; Dunn & Jeste, 2001). Therefore, such persons have diminished capacity to assess the risks and benefits of participating in research and are vulnerable to being exploited.

As suggested by the above definition, the concept of informed consent is guided by certain ethical principles (Luce, 2003). It is primarily supported by the principle of autonomy, or respect for the individual’s capacity for self-determination and exercise of personal choice. Next are the principles of beneficence, which are the professional obligation to promote benefit, and nonmaleficence, the obligation to minimize harm. The last ethical principle is that of justice, or the obligation to provide fair and equitable access. In other words, the research should not preferentially target easily accessible populations, such as persons with mental retardation, institutionalized, or critically ill persons (Bigatello, George, William & Hurford, 2003; Luce 2003).

Given these guiding principles of informed consent, we begin to see more clearly the potential ethical concerns about involving individuals with cognitive impairment in research.

For example, patients with acute stroke can present with dysphasia, dysarthria, a depressed level of consciousness, and/or confusion (Bateman, Meyers, Schumacher, Mangla, & Pile-Spellman, 2003). These problems make it impossible to have any meaningful communication, such as that needed to obtain an informed consent. Likewise, in patients who have schizophrenia, their psychiatric symptoms (e.g., apathy, avolition, inappropriate affect) can be significantly associated with diminished cognitive abilities and decisional capacity (Moser et al., 2003). Thus, there are federal regulations for the protection of research participants (i.e., the code of federal regulation) known as “common rule.” This rule requires additional safeguards (45 CFR 46.116) for research involving “vulnerable populations” including persons who are cognitively impaired (United States Department of Health and Social Services-Office of Human Subjects Protection).

Safeguards

The additional safeguards provided in the common rule to protect cognitively impaired participants in research include advanced informed consent, legal representative, and assent. For example, the regulations require that an institution should consider including one or more persons on its internal review board (IRB) who have knowledge and experience in working with vulnerable populations. Furthermore, it is necessary to measure decision-making capacity of potential participants when cognitive impairment is suspected or possible. Researchers use measurement tools such as the MacArthur Competence Assessment Tool for Clinical Research to assess decision-making capacity.

MacArthur Competence Assessment Tool—Individuals with cognitive impairment may or may not have the capacity to consent to participate in research. For example, they may not be able to process the information. Therefore, potential participants who have a questionable capacity to consent undergo an evaluative test using tools such as the MacArthur Competence Assessment Tool for Clinical Research (Carpenter et al., 2000; Karlawish, 2003). This tool assesses four elements of decisional capacity that are related to the generally applied legal standards for competence to consent to treatment and research, including the ability to: (a) understand relevant research information, (b) appreciate the consequences of one’s participation; (c) reason about the information in a decisional process, and (d) express a choice of whether to participate or not (Carpenter et al., 2000; Moser et al, 2002; Alzheimer’s Association, 2004). A second tool, called Evaluation to Sign Consent, is briefer than the MacArthur Competence Assessment Tool and assesses only understanding of informed consent information (Moser et al, 2002).

To provide consent for research participation, a participant has to: (a) be alert and able to communicate and explain, at a minimum, what their participation entails, (b) understand what the significant risks and benefits are, (c) understand what to do if he or she experiences distress or discomfort, and (d) understand how to withdraw from the study (UCLA, Policy 24: Special Subjects Populations: Cognitively Impaired, 2007). Even then, informed consent is an ongoing process. Therefore, determinations of capacity to provide continuing consent have to be made in an ongoing manner in cases involving participants with questionable cognitive capability. This is especially relevant since their competence may fluctuate. Competence is defined as capacity to act on one’s own behalf, to understand the information presented, to appreciate the consequences of acting on that information, and to make a choice (UCLA, Policy 24: Special Subjects Populations: Cognitively Impaired, 2007). Individuals who do not have the capacity to provide consent or who lose the capacity to provide continuing informed consent are usually excluded from a research study. Exceptions to this rule can occur when an Institutional Review Board (IRB) has granted a waiver of informed consent, there is an advanced informed consent, or there is informed consent of a proxy or legally authorized representative (Alzheimer’s Association, 2004; UCLA, Policy

24: Special Subjects Populations: Cognitively Impaired, 2007). A fuller description of waiver of informed consent, advanced informed consent, and informed consent of a proxy or legal representative follows below.

Waiver of informed consent—A waiver of informed consent is granted in designated emergency cases, such as when a patient is brought in with cardiac arrest. Bigatello and colleagues (2003) noted that, during such emergency conditions, time constraints related to physiologic and emotional factors may compromise the patient's autonomy. Yet, some entire populations can only be studied under emergency conditions. Therefore, research conducted in these situations, such as cardiac research, may require waiver of consent altogether. For example, the health care providers may administer an investigational treatment that has the potential to benefit the patient. European legislature allows for a "deferred" consent, in which case, an assent or consent maybe required once the next of kin shows up or the patient becomes conscious (Lemaire, 2006).

Advance informed consent—In cases in which participants can be recruited before a predictable loss of capacity occurs, advance informed consent may be obtained (Karlawish, 2003). For example, a person who has a genetic predisposition for Alzheimer disease may give an informed consent to participate in a relevant study before onset of illness (Dukoff & Sunderland, 1997). Usually, formal diagnosis of Alzheimer disease is made when mild to moderate symptoms of cognitive impairment begin to appear. Given the disease's predictable decline of cognitive abilities and associated diminished decision-making capacity, researchers may also ask the participant to designate a person in advance who will serve as his or her proxy during the course of the research (Karlawish, 2003).

Durable Power of Attorney or Proxy Decision Making—The National Institutes of Health (NIH), borrowing from the legal world, has recognized a durable power of attorney to provide surrogate decision-making in research with cognitively impaired individuals (Alzheimer's Association, 2004; Dukoff & Sunderland, 1997; Karlawish, 2003). NIH policy on durable power of attorney is for clinical research that involves participants who may be at risk for or have cognitive impairments and is based on three central issues: (a) potential risk to the patient, (b) cognitive status of the patient, and (c) the potential benefit for the patient (Dukoff & Sunderland, 1997). The purpose of these categories is to build varying degrees of safeguards for patients based on the risk-benefit ratio of the study (Alzheimer's Association, 2004; Dukoff & Sunderland, 1997). The durable power of attorney is a legal form signed by both the patient and a witness. It allows a proxy, who is chosen before the patient experiences an onset of severe symptoms or loss of cognitive capacity, but not necessarily before the onset of illness. The proxy may perform a dual role: make decisions regarding health care and /or make research choices. While serving as the health care proxy, the person assigned the durable power of attorney acts primarily on behalf of the patient's best medical interest, but as the research proxy, this person may agree to enroll the patient in a research study that does not offer the patient any medical benefit but is consistent/grounded in the presumed wishes and past behavior of the patient (Dukoff & Sunderland, 1997; Karlawish, 2003).

But who is legally authorized to provide consent on behalf of a prospective participant? A legal representative is an individual or judicial body authorized by law to consent on behalf of a prospective research participant to participate in procedures involved in research. Most states have not addressed this question (Karlawish, 2003). However, in a sample of 79 patients with mild to moderate-stage Alzheimer disease that were involved in a research study with the National Institute of Mental Health (NIMH), 78 had assigned durable power of attorney to someone: 67% to spouses, 28% to an adult child, 3% to siblings, and 1% to an adult grandchild (Dukoff & Sunderland, 1997; Lemaire, 2006). An assent is typically

obtained in addition to a written agreement by durable power of attorney (Alzheimer's Association, 2004; Dukoff & Sunderland, 1997).

Assent—Assent involves less understanding than consent, but is a critical component in the process of consent in the context of the durable power of attorney. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research has stated that, “assent describes the authorization by an individual who is functional, but whose capacity to understand and judge is impaired by illness or institutionalization” (Dukoff & Sunderland, 1997, p. 1072). In other words, each patient must initially give an informed consent, but subsequently may continue to give only an oral and behavioral assent. For example, in the Alzheimer study of NIMH, patients in middle to later stage of the disease typically lacked the capacity to understand all of the information in the informed consent. However, they were allowed to continue to participate in the research if the patient had previously participated in this research, had a predetermined surrogate decision-maker, behaviorally cooperated, and if the surrogate decision-maker consented to the research (Dukoff & Sunderland, 1997; Alzheimer's Association, 2004). These additional safeguards are beneficial and serve the intended purpose of minimizing undue coercion of participants with cognitive impairment, but there are existing gaps or limitations.

Existing gaps in federal regulation

There are reports of gaps in the current code of federal regulations (CFR) in general. Identified gaps specific to patients with cognitive impairment also exist (Alzheimer's Association, 2004; Maschke, 2008). The federal government funds research to improve the lives of subjects who are cognitively impaired. However, it has not provided explicit guidelines to guide investigators in ethical conduct of research with such persons (Bateman et al., 2003; Bigatello, George, William & Hurford, 2003; Karlawish, 2003; Luce, 2003). States vary on the specifics of when a patient who has cognitive impairment may be enrolled in a research study. For example, the Health Care Decisions Act of Maryland indicates that a health care proxy may enroll a patient in research as long as it offers direct medical benefit (Alzheimer's Association, 2004; Dukoff & Sunderland, 1997). Another regulatory gap is related to the question of how to assess decision-making capacity (Maschke, 2008). Maschke (2008) reported that researchers are attempting to develop valid and reliable instruments or tools. But it is unclear how widely they should be used and if their use should be mandated when participants are recruited for clinical trials. Further, federal regulations have not clearly defined “legally authorized representative” (Bateman et al., 2003; Bigatello, George, William & Hurford, 2003; Karlawish, 2003; Maschke, 2008). Consequently, states vary on who may serve as a legally authorized representative. For example, the state of Arizona has designated persons who can serve in this role for research involving health care procedures and for research that does not involve health care procedures (Alzheimer's Association, 2004). Health care procedures may involve the participant's health care agent, legal guardian or conservator, spouse, adult child, parent, domestic partner, sibling, or close friend in that order. If the research does not involve health care procedures, the legally authorized representative may be any those mentioned above (UCLA, Policy 24: Special Subjects Populations: Cognitively Impaired, 2007 (Association, 2004).

There is growing reconsideration of existing safeguards. For example, there is sentiment that safeguards may, in fact, have the unintended effect of hindering advances in the neurosciences that could benefit those with cognitive impairment (Hougham, 2003; 2005). For example, current tools for assessing decision-making capacity were observed to be heavily dependent on verbal skills, and therefore could underestimate the participant's capacity to understand the elements of the informed consent and ability to give their consent to participate (Hougham, 2003). According to Dunn and Jeste (2001), the process of

enhancing informed consent can be achieved by ensuring that informed consent is clearly written, verbally discussed with participants, and adapted to their learning styles (Dunn & Jeste, 2001; Dunn, Palmer, Keehan, Jeste, & Applebaum, 2006). In addition, researchers may enhance decisional capacity by actively including the participant in discussion versus focusing only on surrogate or family members (Hougham, 2003).

Conclusion

It is possible and important to involve persons with cognitive impairment in research. However, their impaired capacity to give informed consent makes them vulnerable to undue influence or coercion. Thus, additional protection and safeguards such as advance informed consent or consent of a legally authorized representative is required. The legally authorized representative needs to be informed about the study and its implications for the individual. He/she must understand their role in providing initial and ongoing consent, and their ability to withdraw the subject when continuation is no longer consistent with that patient's wishes or best interest (Institutional Review Board, Arizona, 2005). It is also crucial for the researcher to keep in mind the need and importance of assent from the participant whenever possible. While guidelines are desirable, there is some concern that they may sometimes unintentionally exclude participants. Given the current gaps in the code of federal regulations, nurse researchers need to be knowledgeable about their respective state rules and regulations regarding: (a) when a participant or patient with cognitive impairment may be enrolled in studies, (b) IRB requirements regarding assessment of decisional capacity, and (c) who may serve as legally authorized representative for participants.

Recommendations

Nurses are in a unique position to promote equitable access to research opportunities for their patients who may have cognitive impairment. Nurses can take certain steps to ensure participants' voluntary consent to participate in research. For example, nurse researchers and clinicians must advocate for proper screening to identify participants who may be at risk for cognitively impairment. Once identified, nurses must advocate for the use of objective measurement tools to assess for decision-making capacity of these participants. For participants who have the decision-making capacity to consent, the nurse researcher may enhance the informed consent process by strategically providing information about the research in very simple, clear, and organized format that incorporates the participants learning style. Such advocacy and educational interventions will minimize, and hopefully prevent any undue coercion while providing equitable access to research participation for individuals with cognitive impairment. Research with cognitively impaired participants helps generate biomedical data required to improve our understanding of illnesses associated with cognitive impairment and the development of effective treatments.

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Biography

Ms. Oruche is a third year pre-doctoral fellow at the Indiana University School of Nursing in Indianapolis. This article was completed in partial fulfillment of training in the ethical conduct of research for the Ruth Kirschstein National Service Award. After obtaining a master's degree in child and adolescent psychiatric-mental health nursing, she practiced for eight years as clinical nurse specialist before deciding to return for a PhD. Her dissertation is titled "Predictors of treatment response for adolescents with serious emotional disturbance".